Time to re-appraise the role of alpha-1 adrenoceptor antagonists in the management of hypertension?

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The role of alpha-1 adrenoceptor antagonists (alpha-blockers) in the management of hypertension continues to evolve. Recent data support their use as add-on therapy in uncontrolled hypertension when used in combination with all other major classes of antihypertensive drug and there is increasing evidence suggesting that they have modest but significant beneficial effects on lipid and glucose metabolism. The availability of extended-release formulations has contributed to an excellent tolerability profile. New data from an observational analysis of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) suggest that doxazosin gastrointestinal therapeutic system (GITS) used as a third-line antihypertensive agent lowered blood pressure and caused modest reductions in plasma lipids. Furthermore, use of doxazosin in ASCOT was not associated with an increased risk of heart failure, in contrast to the earlier finding of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Overall, currently available data support the use of alpha-blockers as safe, well tolerated and effective add-on antihypertensive drugs, which have additional favourable metabolic effects. *J Hypertens* 28:1796–1803
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Journal of Hypertension 2010, **28**:1796–1803

Keywords: alpha-blockers, doxazosin, gastrointestinal therapeutic system, hypertension, metabolic effects

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; Apo, apolipoprotein; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BP, blood pressure; CCB, calcium channel blocker; CHD, coronary heart disease; CHF, congestive heart failure; C_{max}, maximum concentration; C_{min}, minimum concentration; GATES, Doxazosin GITS as Add-on Therapy in Hypertension: an Efficacy and Safety Study; GITS, gastrointestinal therapeutic system; HALT, Hypertension and Lipid Trial; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL-C, low-density lipoprotein cholesterol; MCR, metabolic clearance rate; NICE, National Institute for Health and Clinical Excellence; NS, no significant change; SNS, sympathetic nervous system; SSPG, steady-state plasma glucose; T_{max}, time to maximum concentration; TOMHS, Treatment of Mild Hypertension Study; Total-C, total cholesterol

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Received 14 January 2010 **Revised** 6 April 2010
Accepted 29 April 2010

Introduction

Selective alpha-1 adrenoceptor antagonists (alpha-blockers) effectively lower blood pressure (BP) when used either as monotherapy or in combination with other drugs, including diuretics, beta-blockers, calcium channel blockers (CCBs) and angiotensin-converting enzyme (ACE) inhibitors [1–9]. In addition, they have been shown to have favourable effects on the metabolic profiles of patients with hypertension [3,4,10–19]. Beyond hypertension, they have a role in relieving symptoms of bladder outflow obstruction due to benign prostatic hyperplasia [20].

The Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT) suggested that doxazosin, the most commonly used alpha-blocker, was associated with less effective BP control than chlorthalidone when used as first-line therapy. The doxazosin treatment arm of the study was terminated prematurely due to a significantly higher incidence of combined major cardiovascular disease events, particularly an increased risk of congestive heart failure (CHF), among those randomized to doxazosin compared with chlorthalidone [21]. Consequently, in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines, alpha-blockers were not recommended for the routine treatment of hypertension [22]. This has had a major impact on their use for the treatment of hypertension worldwide.

Recent data on the mechanism of action of alpha-blockers have emerged from experimental studies [23,24] and new clinical studies have confirmed their BP-lowering efficacy [25,26]. Results of an observational analysis from the Anglo-Scandinavian Cardiac Outcomes Trial

0263-6352 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/HJH.0b013e32833b912c

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(ASCOT) [27] have demonstrated the effectiveness of doxazosin and called into question the conclusions of the ALLHAT investigators, prompting a reappraisal of the role of alpha-blockers for the treatment of hypertension.

The clinical narrative review presents an update on the evolving role of alpha-blockers in the management of hypertension. Clinical data on all selective alpha-1 blockers are included, with most data available for doxazosin, the principal reference agent for the class and the alpha-blocker most commonly used for the treatment of hypertension.

Mechanism of action of alpha-blockers

Cardiovascular regulation by the sympathetic nervous system (SNS) is mediated via activation of one or more subtypes of the adrenergic receptor family, including alpha-1 and alpha-2 receptors, classified according to their response to epinephrine and norepinephrine. Blockade of alpha-1 receptors provides a rational approach to the treatment of hypertension by inhibiting the binding of noradrenaline, thereby promoting smooth muscle cell relaxation, reduced vascular tone and decreased peripheral resistance [28]. Early tolerability issues, for example, due to postural hypotension associated with unfavourable pharmacokinetics of immediate-release drugs, have been largely overcome by the development of controlled-release formulations, such as prazosin and doxazosin gastrointestinal therapeutic system (GITS) [29–32]. Such formulations have been designed to improve the drugs' pharmacokinetic profiles and to minimize side effects by slowing absorption and reducing fluctuations in plasma concentration [30]. The pharmacokinetic characteristics of standard and long-acting formulations of alpha-blockers commonly prescribed for the treatment of hypertension are shown in Table 1 [29–32].

Alpha-blockers and blood pressure control

The BP-lowering effects of selective alpha-blockers have been extensively studied, both as monotherapy and in combination with other antihypertensive drug classes.

Table 1 Pharmacokinetic characteristics of standard and long-acting formulations of selective alpha-1 receptor antagonists

Drug	Characteristic	Standard	GITS
Terazosin [29]	T_{max}	1 mg; 1.7 h	–
	C_{max}	1 mg; 15.5 ng/ml	–
Prazosin [31]	Mean residence time	4 mg; 10.8 h	2.5 mg; 21.6 h 5 mg; 22.5 h
Doxazosin [32]	T_{max}	4 mg; 3.7 h 8 mg; 3.9 h	4 mg; 8.2 h 8 mg; 9.1 h
	C_{max}	4 mg; 29.3 ng/ml 8 mg; 66.8 ng/ml	4 mg; 11.3 ng/ml 8 mg; 28.0 ng/ml
	C_{min}	4 mg; 7.4 ng/ml 8 mg; 19.0 ng/ml	4 mg; 6.4 ng/ml 8 mg; 17.8 ng/ml

T_{max}, time to maximum concentration; C_{max}, maximum concentration; C_{min}, minimum concentration; GITS, gastrointestinal therapeutic system.

Studies of prazosin, terazosin, alfuzosin and doxazosin have reported similar BP-lowering efficacy to other therapies when used as monotherapy [1–8]. Following 12 weeks of treatment, standard-release formulations of both prazosin and doxazosin decreased BP in approximately 70% of patients with hypertension, with no difference between treatments [1]. Alfuzosin (not licensed for use in hypertension in the UK or US) was as effective as propanolol when used first line [2]. In a large community-based study, terazosin monotherapy significantly lowered BP with similar efficacy to diuretics, beta-blockers, CCBs and ACE inhibitors; among patients who had not responded to monotherapy with these other drugs, the addition of terazosin resulted in significant BP reductions [3]. Prazosin GITS was shown to have similar BP-lowering efficacy to enalapril in patients with hypertension and diabetes [4]. After 4 years of follow-up in the randomized Treatment of Mild Hypertension Study (TOMHS), initial therapy with standard-release doxazosin (1–2 mg per day) reduced systolic and diastolic BP by 13.4 and 11.2 mmHg, respectively, compared with mean reductions of 8.6 mmHg for both systolic and diastolic BP among those who received placebo [5]. In a 12-week placebo-controlled trial, the Doxazosin Investigators' Study Group found that 68 and 64% of patients with mild-to-moderate hypertension achieved BP targets with standard (1–8 mg per day) and GITS (4–8 mg per day) formulations of doxazosin, respectively, compared with 36% in the placebo group [6]. Other trials of doxazosin monotherapy (both standard and GITS formulations) have demonstrated significant BP reductions with a favourable safety profile [7,8] and doxazosin has been shown to be effective and well tolerated as add-on therapy in uncontrolled hypertension [9].

The timing of doses of alpha-blockers may affect their efficacy. Doxazosin GITS achieved more effective 24-h BP control when administered (either as add-on or monotherapy) at night rather than in the morning [33]. In this 3-month study, a single dose of doxazosin GITS administered at bedtime achieved significantly better 24-h BP control compared with morning dosing, possibly by more effectively reducing the prewaking activation of the SNS. In a substudy of the Hypertension and Lipid Trial (HALT), evening dosing with doxazosin reduced both daytime and night-time systolic and diastolic BP, with potentially favourable effects on nocturnal BP-dipping patterns [34].

Metabolic actions of alpha-blockers

In addition to lowering BP, alpha-blockers have been shown to exert a variety of potentially beneficial effects on lipid and glucose metabolism. These include reduced total cholesterol, low-density lipoprotein (LDL) cholesterol and apolipoprotein (Apo) B concentrations, reduced oxidation of LDL cholesterol, increased high-density lipoprotein (HDL) cholesterol and Apo A-1 concentrations,

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reduced hyperinsulinaemia and an improvement in glucose tolerance [3,4,10–19]. The metabolic effects of alpha-blockers used as monotherapy in recent trials that included at least 100 patients are summarized in Table 2. Favourable effects on lipid profiles have also been demonstrated when alpha-blockers have been used in combination with other classes of antihypertensive agents [3] and on insulin sensitivity when used in combination with acarbose in patients with impaired glucose tolerance [19]. The molecular mechanisms underlying the metabolic effects have been explored and recent evidence suggests that doxazosin may increase HDL cholesterol biosynthesis by mechanisms involving gene transcription that are independent of its alpha-1 receptor antagonist properties [24].

Safety and tolerability of alpha-blockers

Alpha-blockers are generally well tolerated and have similar adverse event profiles to other antihypertensive agents [1–4]. Terazosin was well tolerated in more than 16 000 patients with a variety of concomitant diseases, including CHF, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes and obesity [3]. Adverse events were reported in 18% of patients, most frequently dizziness (5%), headache (3%), and asthenia (2%). Only 0.4 and 0.2% of patients experienced syncope and impotence, respectively, and only 2% dropped out of the study because of adverse events. Standard-formulation doxazosin has an incidence of adverse events similar to placebo, with minor adverse effects such as headache and dizziness being most commonly reported [9,25]. In TOMHS, doxazosin compared favourably with other antihypertensive drugs with regard to erectile dysfunction in men; the incidence decreased by 6% compared with a 10% increase among those randomized to chlorthalidone [35]. Doxazosin GITS is also well tolerated [7,8,26] with fewer discontinuations than with the standard formulation or placebo [6].

The impact of ALLHAT

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial was designed to compare the effects of chlorthalidone (a thiazide-like diuretic) with an alpha-blocker (immediate-release doxazosin), a CCB or an ACE inhibitor among hypertensive patients (aged $\geq$55 years with at least one other vascular risk factor) [21]. Overall, 42 424 participants were randomized, of whom 15 268 received chlorthalidone and 9067 received doxazosin.

Follow-up was planned for 4–8 years. However, the doxazosin arm of the trial was discontinued prematurely following an interim data safety review. This decision was based on a significantly higher incidence of combined cardiovascular disease events (a secondary endpoint) among participants in the doxazosin arm as well as a low likelihood that a difference in the primary endpoint would be observed by the scheduled trial end [21].

Chlorthalidone provided superior BP-lowering efficacy to doxazosin at the doses used (12.5–25 and 2–8 mg, respectively) with systolic BP lower by an average of 3 mmHg. Neither the primary endpoint of fatal CHD or nonfatal myocardial infarction [relative risk (RR) 1.03, 95% confidence interval (CI), 0.90–1.17] nor total mortality (RR 1.03, 95% CI 0.90–1.15) differed between the two groups. However, major cardiovascular events were 25% more frequent among those assigned doxazosin (RR 1.25, 95% CI 1.17–1.33), a result driven by higher rates of stroke (RR 1.19, 95% CI 1.01–1.40) and particularly CHF (RR 2.04, 95% CI 1.79–2.32).

Interpretation of these data has varied widely. Some concluded that doxazosin should be used only as add-on therapy, whereas one editorial questioned even this use [36]; others, meanwhile, questioned the rationale behind early termination of the trial (which itself may have exaggerated any true difference in outcomes between treatment arms). It has been argued that the observed effects on stroke (as well as some of the effect on heart failure) are potentially consistent with the observed BP differences [37], which themselves may be related to the use of suboptimal doses of the short-acting version of doxazosin.

The heart failure results in particular have provoked much debate. Commentators have questioned the validity of heart failure diagnoses, particularly given that the high rates of heart failure observed (2.8 and 5.4% in the chlorthalidone and doxazosin limbs, respectively [21]) were not associated with excess mortality, either in the doxazosin arm or in comparison to other studies [37]. Heart failure was not an independent trial endpoint and events were fully validated retrospectively only in a small subgroup of 50 cases of fatal or hospitalized heart failure. Among these relatively severe cases, there were insufficient data for definitive review in 11 patients and the diagnosis was confirmed in 33 of the remaining 39 cases (85%) [38]. Overall, therefore, the diagnosis of heart failure was only validated in 66% of a sample of the most serious cases and inaccuracies in diagnosis remains a potential source of error. It has been postulated that the early divergence of the event curves for heart failure may represent the unmasking of symptoms of heart failure (e.g. peripheral oedema) due to withdrawal of drugs (presumably mainly diuretics) in the 90% of participants who were taking antihypertensive therapy prior to randomization [37].

New data on blood pressure-lowering efficacy of doxazosin GITS

In the randomized, double-blind Doxazosin GITS as Add-on Therapy in Hypertension: an Efficacy and Safety (GATES) Study, doxazosin GITS (4 mg/day titrated to 8 mg/day if required) or matched placebo was added to existing antihypertensive therapy of patients with uncontrolled BP. After 6 weeks, BP control (<140/90 mmHg)

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Table 2 Summary of metabolic effects of selective alpha-1 receptor antagonists used as monotherapy in trials that included at least 100 participants

Study	Patients	Treatment and duration	Effect on metabolic parameters				
			Total cholesterol	LDL-cholesterol	HDL-cholesterol	Triglycerides	Glucose
Itskovitz (1994) [3]	16 917 patients with hypertension, including 7808 with no previous antihypertensive treatment and 3928 switched to terazosin	Terazosin (baseline to 12 weeks)					
		[a]No previous antihypertensive treatment	5.0% ↓	7.6% ↓	NS	6.1% ↓	
		[a]Switched to terazosin from:					
		Diuretic	6.3% ↓		NS	12.1% ↓	
		BB	5.9% ↓		4.0% ↑	11.8% ↓	
		CCB	5.7% ↓		NS	8.3% ↓	
		ACE-I	5.0% ↓		NS	NS	
HALT study (1996) [13]	851 patients with hypertension	Doxazosin from baseline to 16 weeks	2.7% ↓	2.4% ↓	NS	3.4% ↓	
TOMHS (1996) [14]	902 patients with diastolic hypertension	Doxazosin from baseline; average change over 4 years	6.1% ↓	7.1% ↓	5.2% ↑ (NS vs. placebo)	19% ↓ (NS vs. placebo)	
		Doxazosin compared with acebutolol, amlodipine, chlorthalidone, and enalapril; average change over 4 years	Only doxazosin ↓ by 6.1%	Doxazosin ↓ by 7.1% and acebutolol ↓ by 6.4%	HDL-C/Total-C % - only doxazosin ↑ by 2.6%; other drugs NS	NS all drugs	
Daae and Westlie (1998) [15]	228 patients with hypertension	From baseline to year 5:					
		Doxazosin	3.5% ↓		NS	NS	
		Atenolol	4.5% ↓		13% ↓	35% ↑	
Hobbs *et al.* (2005) [18]	160 British South Asians with hypertension	[b]Doxazosin compared with bendroflumethiazide at week 21	Doxazosin ↓	NS	NS	Doxazosin ↓	Doxazosin ↓ fasting glucose
Derosa *et al.* (2006) [19]	107 normotensive patients with impaired glucose tolerance	Doxazosin compared with placebo from baseline to 6 months; all received acarbose	6.5% ↓	9.8% ↓	8.3% ↑	19% ↓	Insulin resistance ↓ (HOMA index 24.4% ↓; fasting plasma insulin 28% ↓)

ACE-I, angiotensin-converting enzyme inhibitor; BB, beta-blocker; CCB, calcium channel blocker; HALT, Hypertension and Lipid Trial; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL-C, low-density lipoprotein cholesterol; NS, no significant change; TG, triglyceride; Total-C, total cholesterol; TOMHS, Treatment of Mild Hypertension Study. [a] Because of the magnitude and complexity of the study, omissions of various data were unavoidable in individual patients and the numbers were less than those recruited; [b] Statistical comparisons between effects of doxazosin and bendroflumethiazide.

was achieved in 37.3% of those randomized to doxazosin compared with 10.7% of those receiving placebo ($P < 0.001$) [26]. The BP-lowering effects were observed in combination with all major classes of antihypertensive agents and the drug was well tolerated.

The ASOCIA ('Add-on') study was a prospective, open-label, noncomparative study conducted among 3631 Spanish patients with uncontrolled hypertension. Participants received doxazosin GITS (4 mg/day titrated to 8 mg/day if required) in addition to existing medication. The proportion reaching target BP (<140/90 mmHg) was 39% after 4 weeks, rising to 61% at week 16. The drug was well tolerated with less than 3% of participants reporting adverse events [39].

The Anglo-Scandinavian Cardiac Outcomes Trial

Blood pressure-lowering efficacy

The Anglo-Scandinavian Cardiac Outcomes Trial was a multicentre, international, randomized trial conducted among 19 257 patients aged 40–79 years with hypertension and additional cardiovascular risk factors but no history of CHD [40]. Participants were randomly assigned an antihypertensive regimen based on either amlodipine or atenolol in place of existing antihypertensive medication. Perindopril or bendroflumethiazide were added to each arm, respectively, in order to achieve target BP (<140/90 mmHg or <130/80 mmHg in those with diabetes). Doxazosin GITS could be added as a common third-line antihypertensive agent (if BP remained uncontrolled despite maximally tolerated doses of first and second-line drugs) but its use was not randomized.

Overall, 11 768 participants received doxazosin GITS. In an observational database analysis, its effects were evaluated among 10 069 patients (mean age 63 years, 79% male, 32% with diabetes) with valid BP measurements before and during treatment [27]. Among this group, doxazosin was initiated a median 8 months [interquartile range (IQR) 3, 24] after randomization and was added to an average of two other antihypertensive drugs; the mean starting and final doses were 4 and 7 mg, respectively. During a median 12 (IQR 4, 31) months of uninterrupted treatment (during which time there were no changes in other antihypertensive drugs or doses), mean BP fell from 159/89 mmHg (SD 18/11) by almost 12/7 mmHg (SD 19/10, $P < 0.0001$). Significant reductions occurred in all patient subgroups and target BP was achieved in 30%. Although these are uncontrolled data, they are nevertheless consistent with other studies of doxazosin GITS used as add-on antihypertensive therapy.

Metabolic effects

Analyses of lipid profiles included 2945 participants with fasting blood samples taken before and during doxazosin treatment, who took no lipid-lowering therapy and had no changes in other antihypertensives between samples [27]. During a median 9 months of uninterrupted doxazosin therapy, there were significant reductions in total cholesterol (0.28 mmol/l; 4.7%), LDL-cholesterol (0.21 mmol/l; 5.5%) and triglycerides (0.17 mmol/l; 9.1%), consistent with previous studies (see Table 2). No change in HDL-cholesterol was observed.

The effects on fasting plasma glucose were analysed in 3409 patients without diabetes prior to starting doxazosin, with fasting blood samples taken before and during doxazosin treatment, and who had no changes in other antihypertensives between samples. During a median 19 months uninterrupted doxazosin therapy, there was a small but significant increase in fasting plasma glucose (mean 0.11 mmol/l; 3.5%). This finding contradicts previous evidence that doxazosin exerts favourable effects on insulin sensitivity and glucose levels [10–12,18,19]. However, compared with those who did not receive doxazosin in ASCOT, recipients of doxazosin had higher systolic BP and fasting plasma glucose at study entry and were more likely to have been randomized to atenolol-based rather than amlodipine-based therapy, all of which predicted new-onset diabetes among the whole ASCOT cohort [41]; the observed rise may therefore merely reflect the natural increase in glucose in such a population.

Safety and tolerability

All 11 768 participants who received doxazosin GITS in ASCOT contributed to analyses of safety and tolerability, accumulating 39 996 patient-years of exposure to the drug [27]. In total, 1055 adverse events in 877 participants (7.5%) resulted in temporary or permanent discontinuation of doxazosin. Of these, the most common events were dizziness (29%), fatigue (13%), headache (9%), vertigo (9%) and oedema (8%). Although the contribution of each drug to the overall tolerability profile of the study treatment regimen cannot be separated, these findings are consistent with other clinical data regarding doxazosin used as add-on therapy [9,26,39]. However, there still remains a relative paucity of data on its long-term safety.

ASCOT, doxazosin and heart failure revisited

In ASCOT, heart failure was a prespecified secondary endpoint with strict diagnostic criteria and all suspected cases were evaluated rigorously by an independent endpoint committee. Crude heart failure rates were 1.51% among those who received doxazosin at any point in the trial and 1.54% among the remainder. Heart failure occurred at a rate of 2.97/1000 person-years during doxazosin use, compared with 2.85/1000 person-years among never users (rate ratio 1.04, 95% CI 0.80–1.36, $P = 0.76$). In an analysis performed in case doxazosin was stopped because of prodromal symptoms of heart failure (e.g. oedema), the rate of heart failure occurring at any point after initiation of doxazosin (whether or not it

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was continued) was 3.34/1000 person-years (rate ratio 1.17, 95% CI 0.92–1.49, $P = 0.20$, compared with never users) [27]. Therefore, although it should be reiterated that these data are nonrandomized, there appeared to be no excess of heart failure during almost 40 000 patient-years exposure to doxazosin GITS. This was despite the fact that recipients of doxazosin had more severe hypertensive disease (higher systolic BP and prevalence of left ventricular hypertrophy) at study entry than the rest of the study population.

The apparent lack of an increased risk of heart failure in ASCOT is at odds with the observation of a doubled risk of CHF among those assigned doxazosin compared with those assigned chlorthalidone in ALLHAT. Whether this difference reflects the inadequacies of observational data in ASCOT (including various possible sources of bias), use of different formulations of doxazosin (modified-release versus short-acting), differences between use of doxazosin as third or first-line therapy, the presence in each randomized arm of ASCOT of a drug systematically used to treat heart failure (ACE inhibitors or diuretics), the effect of withdrawal of existing diuretic therapy prior to randomization in ALLHAT, or differences in the validity of heart failure diagnosis remains unclear. However, whereas standard doxazosin used first-line may have been less effective than chlorthalidone at reducing BP and preventing stroke in ALLHAT, the use of the GITS formulation as third-line therapy in ASCOT was not associated with increased risk of heart failure.

Hypertension treatment guidelines: changing perspectives

As the importance of achieving and maintaining increasingly challenging BP goals has become more apparent in recent years, guidelines have placed increased emphasis placed on combination therapy. Currently, alpha-blockers have only a minor role in national and international guidelines [22,42–45] (Table 3). Their status in future guidelines is uncertain and may depend on greater confidence by prescribers regarding their safety in the add-on setting.

It is worth noting, however, that whereas alpha-blockers may achieve greater endorsement as add-on therapy in the future, confidence in beta-blockers as a first-line option for uncomplicated hypertension is declining. This is due to evidence that they may not be as effective as other classes of drug in reducing cardiovascular events, particularly stroke [46], and that their use is associated with increased risk of developing new-onset diabetes, particularly when used in combination with thiazide diuretics [47]. This has been recognized in the National Institute for Health and Clinical Excellence (NICE) guidelines, which no longer recommend beta-blockers as initial therapy in uncomplicated hypertension [45].

Conclusion

Selective alpha-1 blockers lower BP and, unlike many other antihypertensives, have favourable effects on plasma lipids and glucose. Recent data have provided important information regarding their efficacy, safety and metabolic benefits, particularly of modified release doxazosin used in the add-on setting. These data suggest that doxazosin GITS is an effective third-line antihypertensive when added to a range of other drugs, improves plasma lipid profiles and is well tolerated. Recent evidence also suggests that it is not associated with increased risks of heart failure when used as add-on therapy. Whereas the lack of morbidity and mortality outcome data remains a major drawback, use of alpha-blockers seems justified, particularly in the add-on setting and in patients with metabolic complications such as dyslipidaemia or the metabolic syndrome.

Contributions and acknowledgements

Editorial assistance was provided by Pam Milner, PhD, of PAREXEL, and was funded by Pfizer Inc.

The authors developed the concept of this review during and following their round-table meeting sponsored by Pfizer Inc. in Hong Kong on 29 July 2007. The authors had full content and editorial control. Editorial assistance was funded by Pfizer Inc.

Table 3 Summary of major guidelines for use of alpha-1 adrenoceptor antagonists for hypertension

Guideline	Year	Recommendation for use of alpha-blockers
Seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC 7) [22]	2003	Included in list of oral antihypertensive agents but place in therapy not defined
Joint British Societies, guidelines on prevention of cardiovascular disease in clinical practice (JBS-2) [42]	2005	Benign prostatic hyperplasia (BPH) listed as a compelling indication Caution advised in patients with postural hypotension and heart failure Contraindicated in urinary incontinence
European Society of Hypertension/European Society of Cardiology (ESH/ESC) [43]	2007	Mentioned as frequently used add-on therapy Benign prostatic hyperplasia listed as a specific indication
British Hypertension Society (BHS) [44]	2004	Recommended as 4th-line therapy Benign prostatic hyperplasia listed as a compelling indication
National Institute for Health and Clinical Excellence (NICE) [45]	2006	Recommended as fourth-line therapy

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Conflicts of interest: N.C. reports receiving speaker fees from Pfizer and Novartis and consultancy fees from Servier.

C.-Y.C. reports receiving fees for moderatorship as well as speaker fees from Pfizer, Novartis, Merck-Schering-Plough and AstraZeneca.

F.D.R.H. reports receiving sponsorship or speaker/consulting fees from Astra-Zeneca, Pfizer, Sanofi, Boeringer, Merck, Roche Diagnostics and Takeda and research funding from Pfizer and Roche Diagnostics in past 3 years.

J.-C.W. reports receiving lecture fees from Astra-Zeneca, Novartis, Pfizer, and Servier.

B.W. has received honoraria for lectures at congresses and symposia supported by Pfizer.

T.F., S.J.K. and S.T. report no conflicts of interest.

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